REMARKS

Claims 1-9 are pending in the instant application. Claims 1-6 have been rejected. Claims 1-6 have been objected to. Claims 7-9 have been cancelled as they are drawn to non-elected subject matter. Claims 1-4 have been amended to remove non-elected subject matter. These amendments do not introduce any new subject matter, and support for them can be found in the specification. After entry of this amendment, Claims 1-6 will remain pending.

Rejection of Claims 1-14 and 18 under 35 U.S.C. §103(a)

The Examiner has rejected Claims 1-6 under 35 U.S.C. §103(a) over Breslin et al., US Patent No. 7,234,580 ("the '580 patent") in view of Patani et al., *Chem. Rev.*, 1996, Vol. 96, pp.3147-3176 ("Patani et al."). Specifically the Examiner states:

> One skilled in the art would have found that the claimed compounds and compositions are *prima facie* obvious over the combined prior art teachings. It is because this difference of R^{10} as –H vs. –F was taught and suggested by Patani et al. –F vs. –H replacement as monovalent bioisosteres, and/or by the '580 patent, which suggests that the pyrrolidine ring as R^c can be further optionally substituted with R^{11}, wherein R^{11} as halo (i.e. item 5). In addition, the prior arts and instant application all teach related art as pharmaceutical applications. Therefore, the instantly claimed invention is obviousness [sic].

The Examiner has further rejected Claims 1-6 under 35 U.S.C. §103(a) over Arrington et al., US Patent Application No. 10/517,559 ("the '559 application") in view of Patani et al., *Chem. Rev.*, 1996, Vol. 96, pp.3147-3176 ("Patani et al."). Specifically the Examiner states:

> One skilled in the art would have found that the claimed compounds and compositions are *prima facie* obvious over the combined prior art teachings. It is because this difference of R^{10} as –H vs. –F was taught and suggested by Patani et al. –F vs. –H replacement as monovalent bioisosteres, and/or by the '559 application, which suggests that the pyrrolidine ring as R^c can be further optionally substituted with halo. In addition, the prior arts and instant application all teach related art as pharmaceutical applications. Therefore, the instantly claimed invention is obviousness [sic].

Applicants respectfully traverse this rejection. Drug discovery and design is a complex process involving many variables. The pharmaceutical sciences are unpredictable, and it is difficult to predict the activity of a compound without further testing.

On page 3149, Patani notes that 5-fluoro-2'-deoxyuridylic acid is a successful mimetic because it inhibits thymidylate synthase. Patani further explains that "the increased reactivity of 5-fluoro-2'-deoxyuridylic acid relative to 2'-deoxyuridylic acid us due to the inductive effect of fluorine which results in its covalent binding to the thymidylate synthase." The substitution of fluoro **in this instance** results in enhanced affinity due to the specific relationship of 5-fluoro-2'-deoxyuridylic acid to the thymidylate synthase receptor. Such a specific relationship cannot be generalized for all compounds and all receptors.

The Examiner also points to the compounds of Table 4 on page 3149 wherein the fluoro substituted naphthyl-fused diazepine analogues disclosed displayed stronger binding affinity to the benzodiazepine receptor than the hydrogen analogue. The substitution of fluoro for hydrogen **in this particular class of compounds** (naphthyl-fused diazepine) enhanced binding affinity to **this particular receptor** (benzodiazepine receptor). However, a similar result cannot be expected in every fact pattern for every class of compounds. It cannot be stated that **any** substitution of fluoro for hydrogen on **any** chemical core structure that binds to **any** receptor would yield compounds of stronger binding affinity. In fact, the Patani reference even cautions against such generalizations on page 3151:

> It is important to note that retention of biological activity based on the *in vitro* data can be critical in those instances where differences between bioisosteric analogues exist with regard to *in vivo* parameters which may include absorption, distribution, metabolism, or elimination. While one may only observe retention of activity associated with interaction of drug with the pharmacophore, bioisosteres may differ dramatically in their *in vivo* efficacy.

Applicants do not believe that the Examiner's reasoning applies to the compounds disclosed in the instant application, but should be limited to the specific fact patterns described in Patani. Furthermore, one skilled in the art would not expect compounds that bind to the benzodiazepine receptor to bind to KSP mitotic kinesins.

Accordingly, Applicants respectfully request the rejections of Claims 1-6 under 35 USC §103(a), be withdrawn.

Rejection of Claims 1-14 and 18 for Double Patenting

The Examiner provisionally rejected Claims 1-14 and 18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over US Patent No. 7,235,580 ("the '580 patent"). Applicants respectfully traverse this rejection. The '580 patent does not contain any species that overlap with the instant application. The compounds of the instant invention are required to have either an F or CH_2F substituent at the 3 or 5 position on the pipieridine. The cited compound does not have such substitution; in fact, none of the claimed or exemplified compounds have either an F or CH_2F substituent at the 3 or 5 position on the pipieridine. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Objection of Claims 1-6

The Examiner has objected to Claims 1-6 for containing elected and non-elected subject matter. Applicants have amended Claims 1-6 to remove non-elected subject matter, and this rejection should be rendered moot. Accordingly, Applicants respectfully request that this objection be withdrawn.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By Nicole M Beeler

Nicole M. Beeler
Reg. No. 45,194
Attorney for Applicants

MERCK & CO., INC.
P.O. Box 2000
Rahway, New Jersey 07065-0907
(732) 594-1077

Date: January 29, 2008